NexEos Bio™

Brief Summary

NexEos Bio – Overview

- Founded and managed by the team that successfully developed *reslizumab,* and has worked on eosinophil-mediated inflammation for 20+ years
- Years of research led to the discovery that **eMBP1** is a central actor driving inflammation
  - Released by activated eosinophils, eMBP1 drives inflammation and remains in target tissue much longer than eosinophils (approx. 6 weeks)
- Strong IP in both diagnostics and therapeutics: ***the only company in the world with these diagnostic capabilities***

Diagnostic Program

Binding to eMBP1 to identify and monitor disease

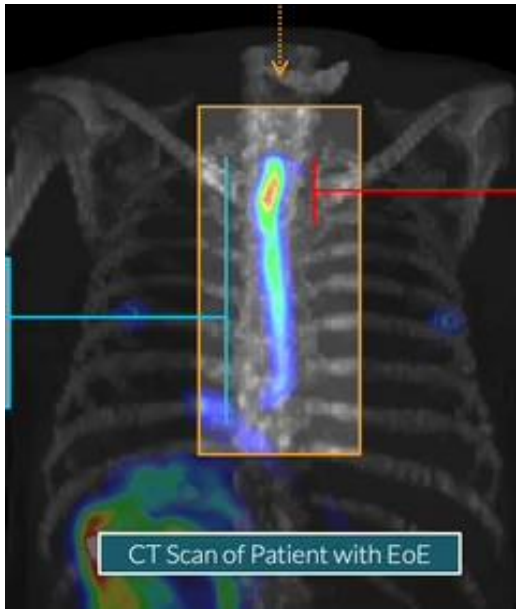
Therapeutic Program

Neutralizing eMBP1 to reduce inflammation, control symptoms

NexEos – Diagnostic Opportunity

NDX33-o (radio-labeled heparin) for detection of eMBP1 inflammation in EoE

NDX33-o, a non-invasive imaging agent, binds to eMBP1 and "lights up" eosinophil-related inflammation in the esophagus → vast opportunities for diagnostics in other areas of the body currently undiagnosable



Heparin (most acidic substance in the body) binds to eMBP1

Established pharmacokinetic and safety profiles – not systemically absorbed when taken orally

Technetium forms a stable complex with radio-labeled heparin (NDX33-o)

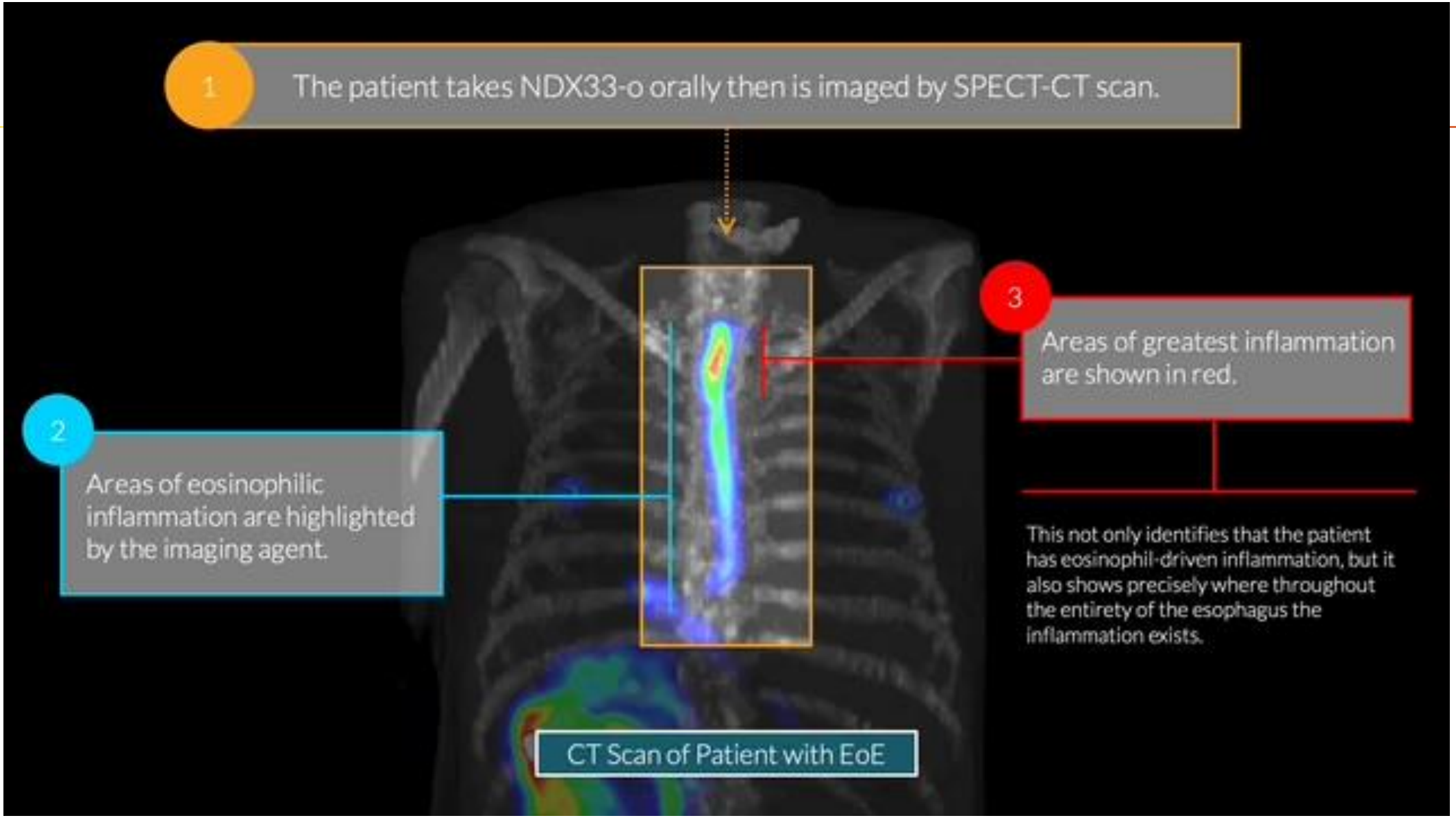
- Proof of concept demonstrated in initial study of 8 EoE patients
- Clearly defined regulatory path
- **CMC supply** for heparin established – US supplier
- Filed IND for NDX33-o
- Rapid path to market for lead diagnostic indication
- **NIH grant ($4M)** further validates science
- Strong granted IP – **issued patents run through 2034**; additional filings pending
- Granted Orphan Drug Designation for EoE; filed for Fast Track, **pending IND opening [January 2021 FDA meeting]**

Scientific Advances

First, non-invasive and visual diagnostic for EoE

Published on false negative for EoE biopsy vs positive read when targeting eMBP1 as marker

Using antibody for eMBP1 extra cellular detection in pathology, proving false negative patients can be positive for EoE Dx


1
The patient takes NDX33-o orally then is imaged by SPECT-CT scan.
2
Areas of eosinophilic inflammation are highlighted by the imaging agent.
3
Areas of greatest inflammation are shown in red.
This not only identifies that the patient has eosinophil-driven inflammation, but it also shows precisely where throughout the entirety of the esophagus the inflammation exists.
CT Scan of Patient with EoE

NexEos Bio

NexEos – Therapeutic Opportunity

NTXf100 and NTXp101: NCEs for neutralizing eMBP1 for treatment of eosinophil-mediated diseases

NTXf100 and NTXp101 have been synthesized to block the cellular destructive effects of eMBP1 and the recruitment of other inflammatory mediators. This forms the basis for NexEos' therapeutic program.

NTXf100

- **Lead therapeutic program – targeted, non-systemic oral and topical as first-line therapy in chronic gastrointestinal and ocular conditions**
- Proprietary, fractionated high molecular weight subtype of heparin to be used as a non-systemic oral solution and/or eye drop
- Rapid path to market for lead indications: non-systemic oral for EoE; topical for atopic keratoconjunctivitis
- **Opportunity for effective, targeted non-systemic oral and topical forms to be used as first-line therapy in GI, nasal and ocular conditions, reserving biologics for patients who have severe disease**

NTXp101

- ***Targeted injectable/inhaled treatment as first-line therapy for mild to moderate chronic disease to further expand therapeutic reach and commercial potential***
- Next Generation product (NTXp101) will allow for systemic and inhaled administration
- Provisional applications filed for composition of matter and methods of use
- ***Opportunity for a next generation therapy with the ability to deliver as injectable/inhaled forms – expands potential to indications such as asthma, HES, CSS***

NexEos Bio

NexEos Bio Pipeline

Robust pipeline of programs for the diagnosis and treatment of eosinophilic diseases

Program	Indication	Preclinical Development	Phase 1	Phase 2
NDX33-o	In vivo imaging agent for diagnosis and management of EoE (adults and pediatrics)			
NDX33-o	In vivo imaging agent for diagnosis and management of additional indications (EGID, eos rhinosinusitis)			
NTXf100	NCE for treatment of eosinophil-driven diseases *(non-systemic oral/topical)* (EoE, EGID, eos rhinosinusitis, eos ocular conditions)			
NTXp101	Proprietary protein for neutralizing eMBP1 inflammation for treatment of eosinophil-driven diseases *(injectable/inhaled agent)*			

DIAGNOSTIC PROGRAM:

8 patients studied under RDRC at University of Utah established clear proof of concept;
NexEos clinical study to be conducted in collaboration with NIH under U44 grant

NDX33-o: To expand beyond EoE into additional eos-mediated diseases

THERAPEUTIC PROGRAM:

Neutralize eMBP1 inflammation across a wide array of eos-mediated diseases

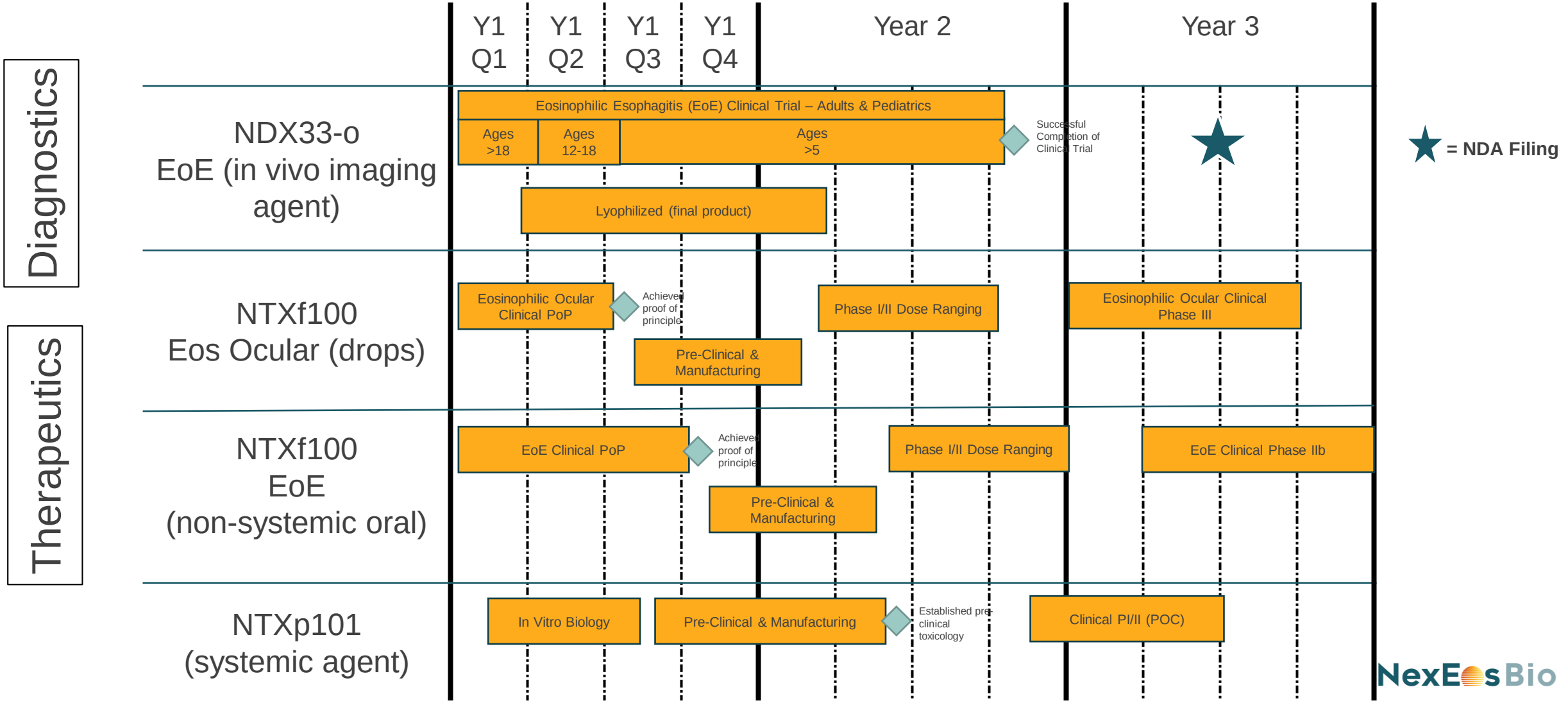
NTXf100: NCE non-systemic oral and topical treatment of eos-mediated diseases

NTXp101: 2nd generation NCE to enable injectable/inhaled delivery

FUNDING REQUIREMENT: $30M, can be traunched $20M/10M based on milestones

NexEos Bio

NexEos Bio: 3-Year Development Plan & Milestones



NexEos Bio™

Summary

NexEos Bio Highlights

Focused on the treatment, management and diagnosis of chronic eosinophilic diseases

- High unmet medical need for eosinophilic disease therapeutics and diagnostics
- Team has worked on eosinophil-mediated inflammation for 20+ years
- Successfully developed anti-IL5 mAb, reslizumab (Cinqair®) for eosinophilic asthma
- New understanding of the effect of eosinophil major basic protein 1 (eMBP1) in eosinophil-mediated inflammatory diseases
  - *Specific radiolabeled diagnostic (NDX33-o) - clear proof of concept in eosinophilic esophagitis (EoE) patients*
    - *potential first, non-invasive diagnostic tool*
    - *new imaging capability - first visual images of eosinophil-driven inflammation*
  - *NDX33-o clinical study to be conducted in collaboration with NIH under SBIR-U44 grant*
  - *Orphan Drug Designation granted for EoE diagnostic*
  - *NTXf100 and NTXp101 synthesized to block cellular destructive effects of eMBP1 and recruitment of other inflammatory mediators. The basis for therapeutic program in mild to moderate, chronic eosinophilic diseases*
    - *Target eMBP1 binding demonstrated in 8 patients through diagnostic program*
  - *Exploring ability to target various diseases with eosinophilic inflammation: eosinophilic GI disorders (EGIDs), such as EoE, eos gastroenteritis, and eos colitis; eos conjunctivitis; eos rhinosinusitis*
- Strong IP estate in both diagnostics and therapeutics

NexEos Bio radiolabeled diagnostic of SPECT/CT image of eosinophil-driven inflammation

NexEos Bio

NexEos Bio Pipeline

Robust pipeline of programs for the diagnosis and treatment of eosinophilic diseases

Program	Indication	Preclinical Development	Phase 1	Phase 2
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NexEos Bio

NexEos Bio: History of the Team

- NexEos is a team of experienced large pharma and biotech entrepreneurs
- A track record of clinical success and outstanding investor returns
- A team with relevant experience in eosinophil-mediated diseases, from discovery and pre-clinical to clinical development
- Previously leaders in the successful development of the anti-IL5 monoclonal antibody, reslizumab (Cinqair®), approved for eosinophilic asthma

7 exits - all with positive returns
6 companies acquired and 1 IPO
4 FDA - approved therapies

trigenesis THERAPEUTICS

Dermatology
Acquired by
Dr. Reddy's
2004

CEPTION therapeutics

CINQAIR Anti IL5
Eos Asthma
FDA Approved
Acquired by Cephalon
2010

vicept THERAPEUTICS INCORPORATED

RHOFADE
Rosacea
FDA Approved
Acquired by Allergan
2011

CEPTARIS therapeutics

VALCHOR
CTCL (Cancer)
FDA Approved
Acquired by Actelion
2013

ACLARIS THERAPEUTICS

ESKATA
Dermatology
FDA Approved
IPO
2015

akarna THERAPEUTICS

FXR
NASH
Acquired by
Allergan
2016

ONSPIRA™ THERAPEUTICS

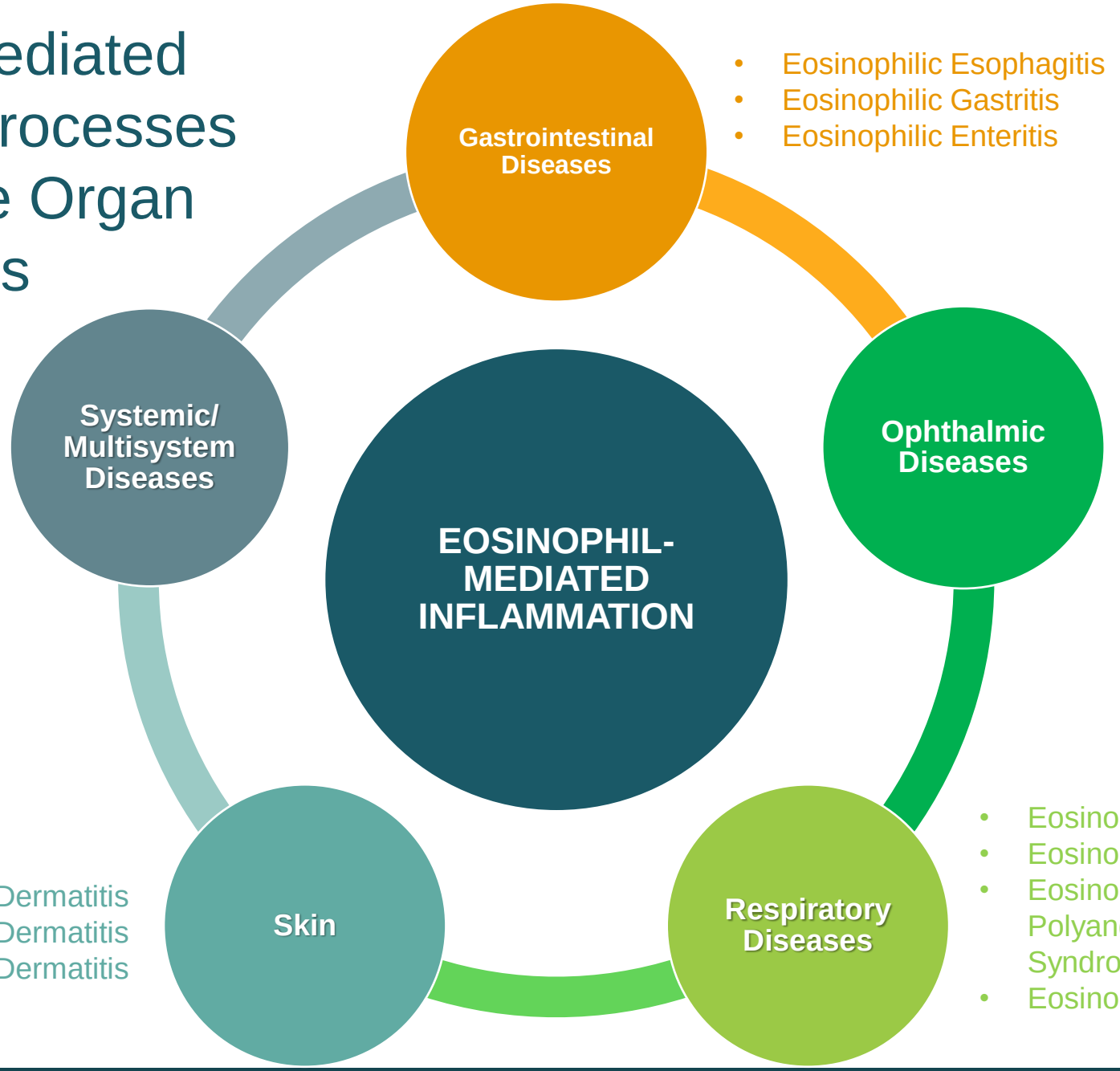
Anti-IL1
Orphan Lung
Acquired by
Altavant
Sciences /
Sumitomo
2019

NexEos Bio

The Scientific Rationale for Targeting eMBP1

NexEosBio™

Eosinophil-Mediated Inflammatory Processes Affect Multiple Organ Systems



- Eosinophilic Esophagitis
- Eosinophilic Gastritis
- Eosinophilic Enteritis

- Atopic Keratoconjunctivitis
- Vernal Keratoconjunctivitis
- Seasonal/Perennial Allergic Conjunctivitis

- Eosinophilic Asthma
- Eosinophilic Bronchitis
- Eosinophilic Granulomatosis with Polyangiitis (Churg-Strauss Syndrome)
- Eosinophilic Rhinosinusitis

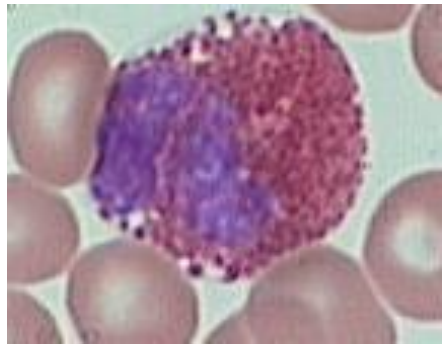
- Atopic Dermatitis
- Chronic Contact Dermatitis
- Urticarial Dermatitis

- Hypereosinophilic Syndrome
- Eosinophilic Fasciitis

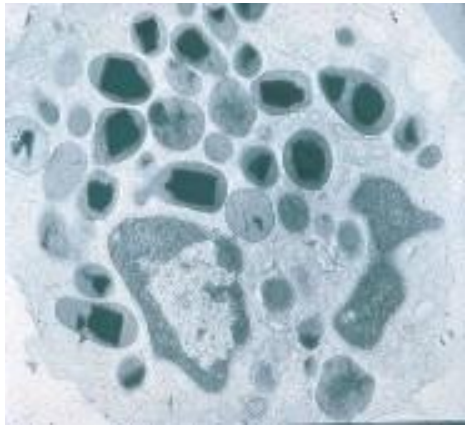
Eosinophil-Related Disease: Shift in the Scientific Paradigm

- Eosinophils are white blood cells
  - Circulate in blood and trafficked to target tissues
  - Prominent in allergic diseases (increasingly prevalent) and parasitic infections (decreasingly prevalent)
- Eosinophil-related diseases increasingly identified (in all organs)
- In several inflammatory conditions, reducing eosinophils has conveyed clinical benefit suggesting increasingly complex roles for eosinophils in disease[1]
  - Research in asthma has elucidated the role of eosinophil-mediated inflammation and the function of eosinophil granule products in the pathogenesis of asthma
  - Currently four FDA-approved therapies for eosinophilic asthma

Peripheral blood eosinophil



Electron micrograph (EM) of tissue eosinophil



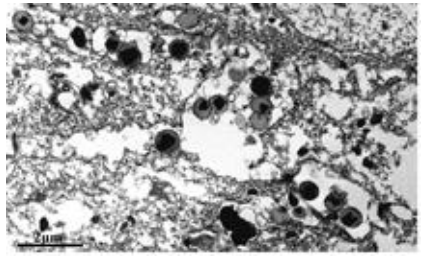
1. Furuta, G.T., Atkins, F.D., Lee, N.A., and Lee, J.J., Changing roles of eosinophils in health and disease. Annals of Allergy, Asthma, and Immunology, 2014, 113 (1): p. 3-8

Eosinophil-Related Disease: Shift in Pathophysiologic Paradigm

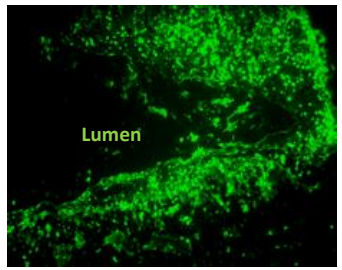
Eosinophils have distinctive cytoplasmic granules

- Eosinophil granule products, especially cationic proteins, are cytotoxic and associated with epithelial damage and hyperplasia across multiple organ systems
- Eosinophil major basic protein 1 (eMBP1) is the granule core and the most abundant granule protein in the cell
  - Toxic - kills cells, bacteria, worms
  - Activates neutrophils, basophils, platelets and other cells
  - Dilates blood vessels and induces bronchial hyperreactivity and spasm
- eMBP1 is deposited extracellularly with cytolytic degranulation of eosinophils, and eMBP1 persists [~6 weeks] in tissue driving inflammation

EM of eosinophil granules deposited extracellularly in EoE



Immunostaining for eMBP1 in EoE epithelium*



eMBP1: Distinctive granule core within eosinophil [pI ~11.4]

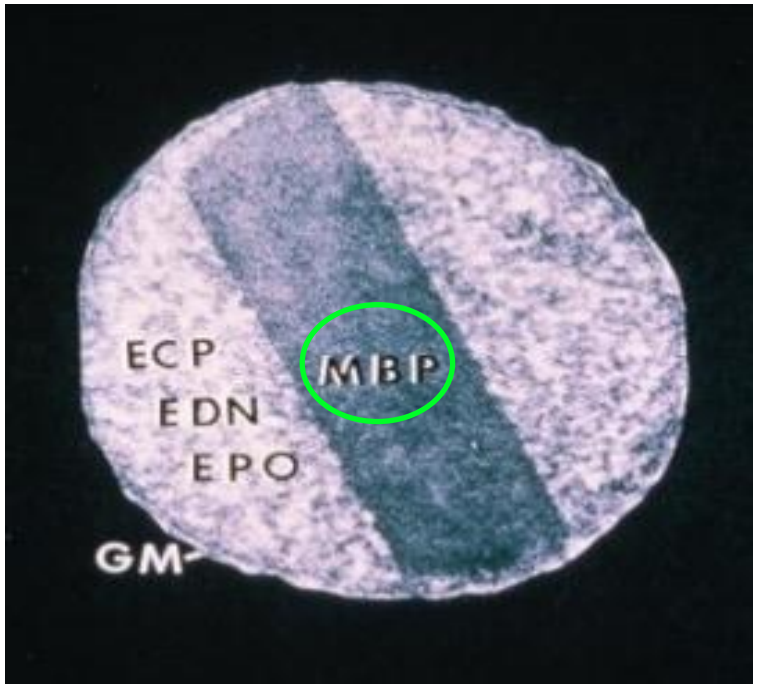


Image obtained from the labs of Drs. Gleich and Leiferman at the University of Utah

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Foundation of NexEos Programs: eMBP1 Target

eMBP1 remains in target tissue much longer than eosinophils

- Years of research led to the discovery that eMBP1 is a central actor driving inflammation
  - Released by activated eosinophils, eMBP1 drives inflammation and remains in target tissue much longer than eosinophils
- Target for diagnostic and therapeutic uses
  - Diagnostic Program: *Binding* to eMBP1 to diagnose and monitor disease
  - Therapeutic Program: *Neutralizing* eMBP1 to reduce inflammation – symptom control, treatment

Therapeutics

eMBP1: A New Target in Treating Eosinophil-Mediated Inflammation

Preclinical Evidence

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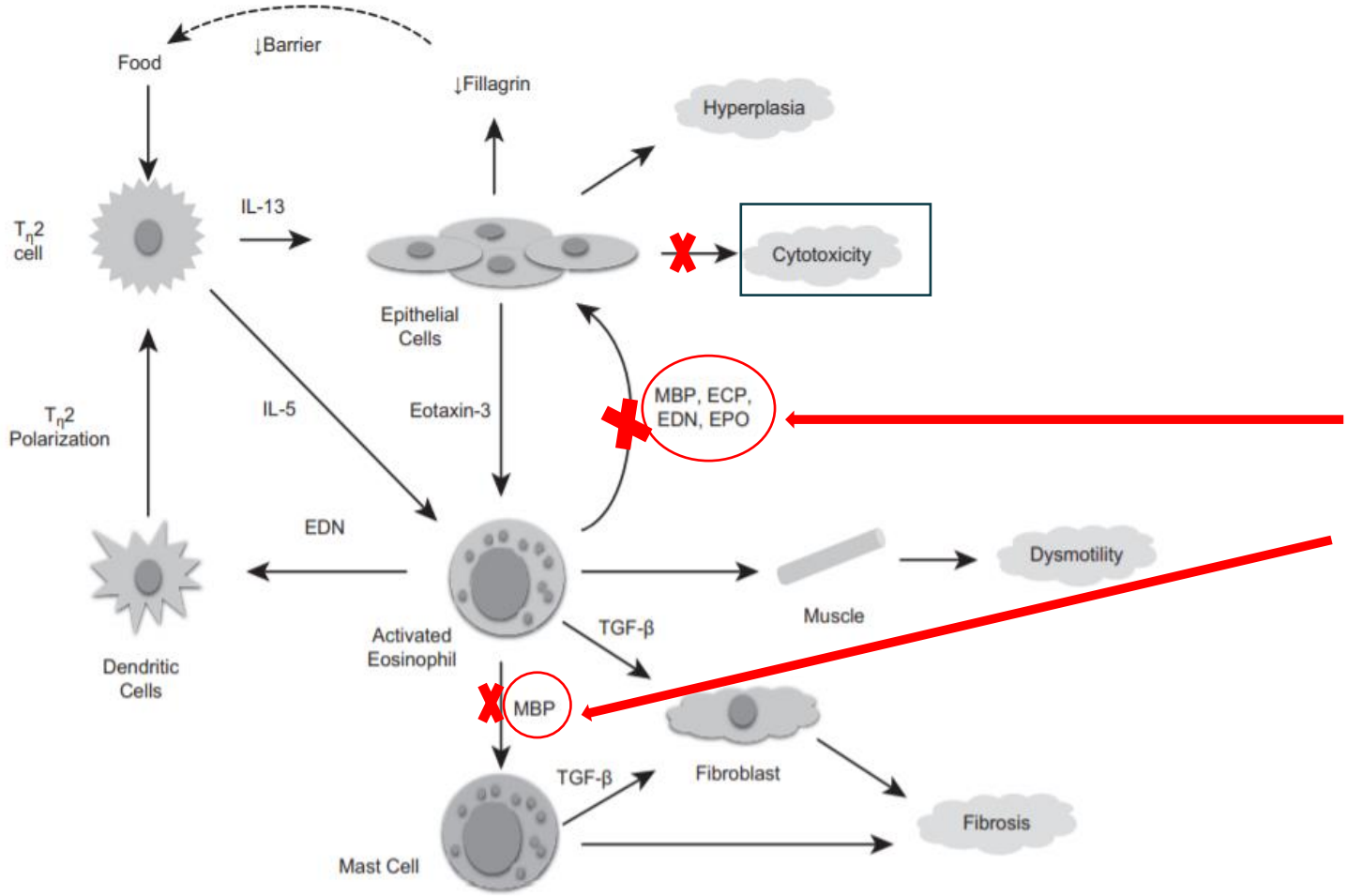
eMBP1 Neutralization: Blockade of Eosinophil Granule Products Demonstrate Anti-Inflammatory Effects



Neutralization of eosinophil granule products reduces cytotoxicity and therefore inflammatory effect on epithelial tissues and cells

Adapted from: Davis BP, Rothenberg ME. Eosinophils and Gastrointestinal Disease. In: Lee JJ, Rosenberg-HF.,editors. *Eosinophils in Health and Disease*. Waltham, MA. Academic Press, Elsevier 2012. p 484-493

NexEos Bio

eMBP1 is a New Target to Affect Clinical Outcomes in Eosinophil-Mediated Inflammation*

- Eosinophil granule products are implicated in the pathogenesis of various target tissues including the lung, gastrointestinal tract, sinuses, skin, and the eye
- Despite new therapies currently on the market for eosinophilic disease, significant unmet need remains
- Neutralization of eosinophil granule proteins disrupts cytotoxic effects on tissues and inhibits the inflammation and cell hyperplasia seen in eosinophil-mediated disease processes
- In preclinical evaluations of both rat[1] and primate[2] models, eMBP1 is directly responsible for an increase in airway responsiveness and bronchoconstriction as seen in clinical presentation of asthmatic patients
- In the antigen-challenged guinea pig model[3], pretreatment with antibody to eMBP1 prevents airway hyperresponsiveness, demonstrating blockade of eMBP1 has anti-inflammatory effects on targeted tissues

1.Uchida DA, Ackerman SJ, Coyle AJ, Larsen GL, Weller PF, Freed J, et al.. Am Rev Respir Dis 1993;147:982e8
2.Gundel RH, Letts LG, Gleich GJ: J Clin Invest 87:1470-1473, April 1991
3.Evans et al. J. Clin. Invest. 1997. 100:2254– 2262

NTXf100 and NTXp101 have been synthesized to block the cellular destructive effects of eMBP1 and the recruitment of other inflammatory mediators. This forms the basis for NexEos' therapeutic program.

* Detailed Pre-clinical Evidence slides are in Appendix, slides 39-44.

NexEos Bio

Therapeutics

NTXf100 and NTXp101 for Eosinophil-Mediated Inflammation

Initial Disease Targets: Gastrointestinal and Ocular Diseases

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NexEos Bio Therapeutic Opportunity

NTXf100 and NTXp101: NCEs for neutralizing eMBP1 for treatment of eosinophil-mediated diseases

- ***NTXf100, lead therapeutic program – targeted, non-systemic oral and topical as first-line therapy in chronic gastrointestinal and ocular conditions***
  - Demonstrated strong binding to eMBP1 in proof of concept, clinical trial for NDX33-o (oral, radiolabeled heparin) in 8 EoE patients
  - Proprietary, fractionated high molecular weight subtype of heparin demonstrates the greatest binding affinity to eMBP1
  - Rapid path to market for lead indications: non-systemic oral for EoE; topical for atopic keratoconjunctivitis
  - Number of additional therapeutic indications can be pursued with targeted delivery
  - CMC supply established – US supplier

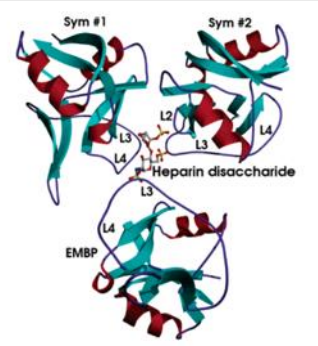
- ***NTXp101 - targeted injectable/inhaled treatment as first-line therapy for mild to moderate chronic disease to further expand therapeutic reach and commercial potential***

- Provisional applications filed for composition of matter and methods of use

Scientific Advances

- *NTXf100 – Fractionated high molecular weight heparin demonstrates the greatest binding affinity to eMBP1*
- *For the first time, NTXp101 – proprietary protein for neutralizing eMBP1 - has been synthesized*
- *NTXp101 – Recombinant protein, made in human embryonic kidney (HEK) cells*

Heparin binds avidly to a specific site on eMBP1



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Summary of Key Eosinophil-mediated Effects in Eosinophilic Esophagitis (EoE)

- NDX33-o (diagnostic agent) binds strikingly to EoE biopsy specimens where eMBP1 is abundantly present throughout luminal epithelium
  - Visual analog assessments and dosimetry measurements correlate with eMBP1 deposition
- Demonstrated binding to eMBP1 in proof of concept, clinical trial for NDX33-o in 8 EoE patients
- Treating EoE and other GI disorders by neutralizing eMBP1 is a rational target
  - Heparin – most acidic (negatively charged) substance in the body binds to eMBP1 (strongly basic and one of the most positively charged substances[1])
  - Heparin is not systemically absorbed in the mucus membranes [no anti-coagulation]
  - Fractionated Heparin (NTXf100) – SPR analysis demonstrates binding affinity greatest to high molecular weight subtype of heparin
  - Neutralizing effects as seen in pre-clinical models develop a strong scientific hypothesis
- Targeted delivery of therapy is most feasible route of administration for heparin-based agent
  - e.g., non-systemic oral for GI conditions, eye drops for ocular, or spray for nasal conditions

1. Saffari et. al, Mayo Clin Proc. 2020;95(3):449-458

NexEos Bio

Summary of Key Eosinophil-Mediated Effects in Inflammatory Bowel Diseases (IBD)

- Eosinophil granule-derived proteins reflect disease activity in IBD
  - Measured fecal EPX (eosinophilic peroxidase) and ECP (eosinophilic cationic protein) concentrations were significantly increased in both active UC and CD in an investigative study of 47 UC, 37 CD and 29 control patients[1]
- A positive correlation is seen between the number of infiltrating eosinophils and disease severity in UC
  - Severe eosinophilic infiltration of lamina propria was noted in histological evaluation of colorectal biopsy specimens from 10 nonresponding (to medical treatment) patients with active UC[2]
- Eosinophils have been found to increase mucosal barrier permeability in UC by releasing MBP and thus contributing to the pathogenesis of IBD
  - In a Th2-mediated mouse colitis model, relative to wild-type mice, eMBP1-deficient mice failed to develop pathologies associated with Th2-mediated colitis, suggesting a direct link between eosinophils and intestinal dysfunction[3]
- In a study of patients exhibiting acute exacerbations, quiescent disease and therapeutically resistant IBD, deposition of extra-cellular MBP was seen in both active and quiescent stages in the clinically responsive group of patients, with greater deposition in active disease, and rarely observed MBP in the refractory group[4]

1. Saitoh O et al. Am J Gastroenterol (1999) 94:3513–20.
2. Zezos P et al. Colorectal Dis (2014) 16
3. Furuta GT, Nieuwenhuis EES, Karhausen J, Gleich G, Blumberg RS, Lee JJ. Am J Physiol Gastrointest Liver Physiol (2005) 289:G890–7. doi:10.1152/ajpgi.00015.2005
4. Smyth CM, Akasheh N, Woods S, Kay E, Morgan RK, et al. (2013) Activated Eosinophils in Association with Enteric Nerves in Inflammatory Bowel Disease. PLoS ONE 8(5): e64216.

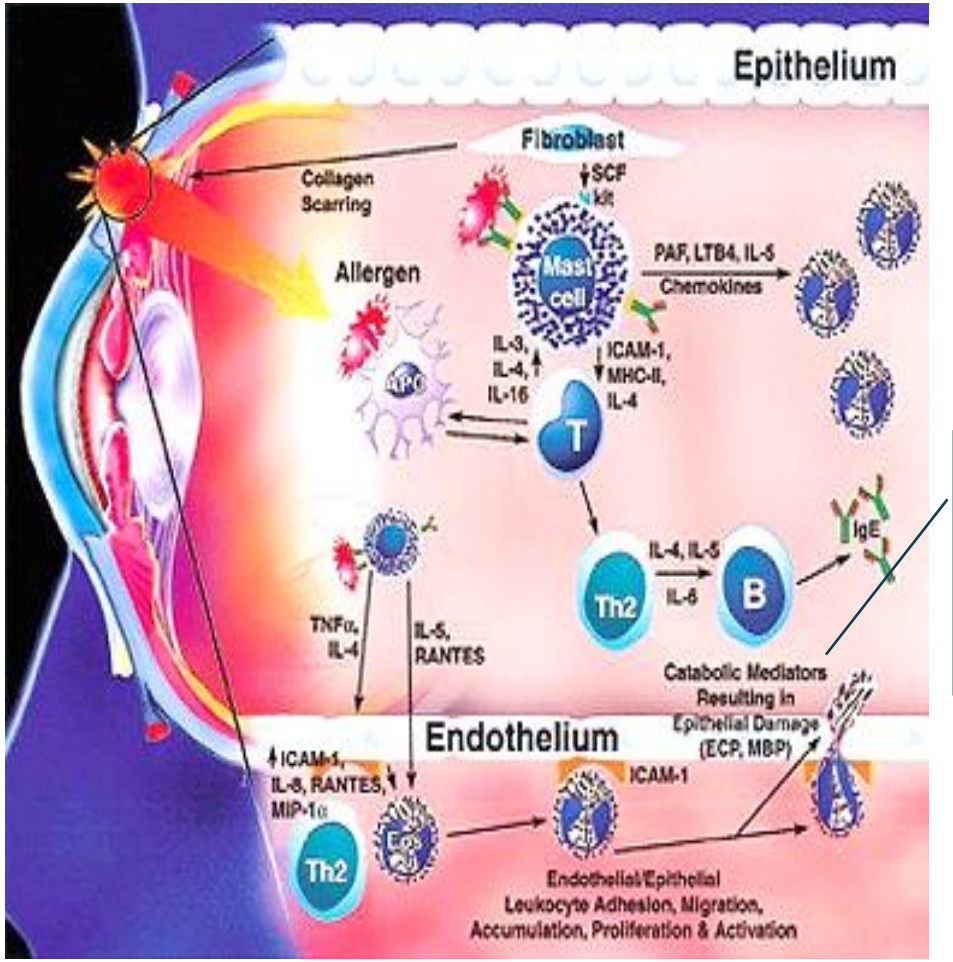
Ocular Disease: Eosinophils and eMBP1

- Diseases clinically recognized as having an allergic pathophysiological component are seasonal and perennial allergic conjunctivitis, vernal conjunctivitis (VKC), and atopic keratoconjunctivitis (AKC)
  - Involvement of eosinophils in these diseases has been explored by analyses of tears and studies of ocular biopsies
- Studies of vernal ulcerations noted in patients with VKC utilizing indirect immunofluorescence assays show eMBP1 deposition in the cornea[1]
- Further clinical investigations evaluating conjunctival biopsy specimens from patients with VKC, giant papillary conjunctivitis, and control have shown significantly greater amounts of eMBP1 deposition in tissues[2]

Differential diagnosis of occular allergy						
	SAC	PAC	VKC	AKC	GPC	CDC
Eosinophils in swab	Frequent	Very frequent	Characteristic	Characteristic	Not frequent	Not frequent

Abbreviations: SAC, seasonal allergy conjunctivitis; PAC, perennial allergic conjunctivitis; VKC, vernal keratoconjunctivitis; AKC, atopic keratoconjunctivitis; GPC, giant papillary conjunctivitis; CDC, contact dermatoconjunctivitis

Adapted from: MC Sánchez et al. J Investig Allergol Clin Immunol 2011; Vol. 21, Suppl. 2: 1-19



Catabolic Mediators Resulting in Epithelial Damage (ECP, MBP)

Adapted from: Bielory L. J Allergy Clin Immunol 2000;106:805-16

1. Trocmé SD et al. American Journal of Ophthalmology.1993;115:640-643
2. Trocmé et al. American Journal of Ophthalmology. 1989;108:57-63

NexEos Bio

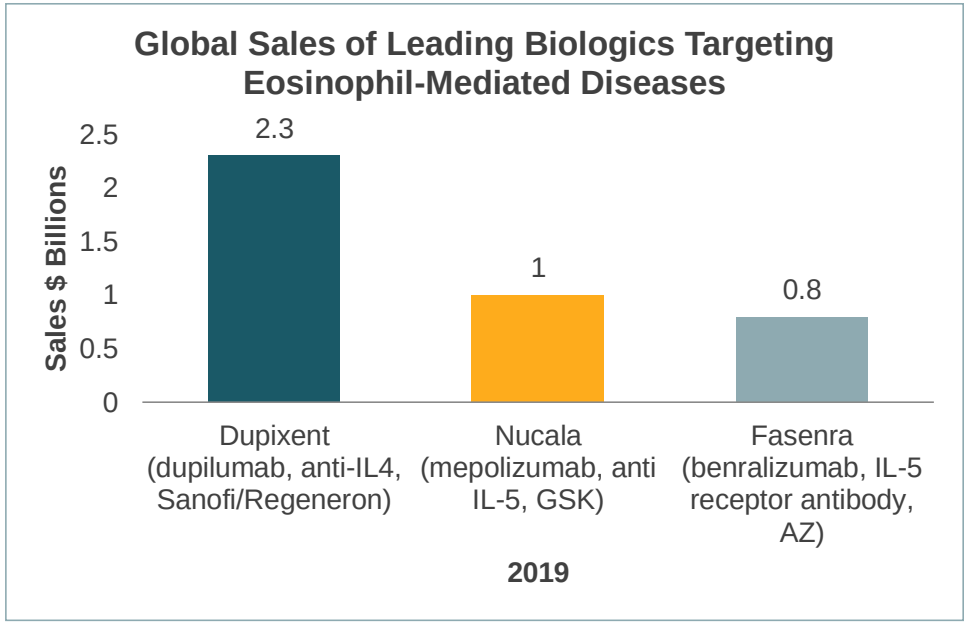
Therapeutics

Commercial Opportunity: Neutralizing eMBP1 in Eosinophil-Mediated Inflammatory Diseases

NexEosBio™

Biologics Have Built a Significant Market for Eosinophil-Driven Inflammation

- Evolving Market - biologics targeting eosinophil-mediated diseases are driving large market value
  - Dupixent approved for: Atopic dermatitis (Mar 2017), mod-severe eos asthma (Oct 2018), and chronic rhinosinusitis w/nasal polyps (Jun 2019)
  - Nucala approved for: Eos asthma (Nov 2015), Churg-Strauss Syndrome [aka eos granulomatosis with polyangiitis] (2017), and Hyper Eosinophilic Syndrome (HES) (Sept 2020)
    - 36% growth in 2019
    - Currently pursuing nasal polyps and COPD
  - Fasenra approved for: Eos asthma (Nov 2017)
    - 65% YoY growth in 2019
    - Currently pursuing COPD, nasal polyps, HES and Churg-Strauss Syndrome
- *NTXf100 - Opportunity for effective, targeted non-systemic oral and topical forms to be used as first-line therapy in GI, nasal and ocular conditions, reserving biologics for patients who have severe disease*
- *NTXp101 - Opportunity for a next generation therapy with the ability to deliver as injectable/inhaled forms – expands potential to indications such as asthma, HES, CSS*

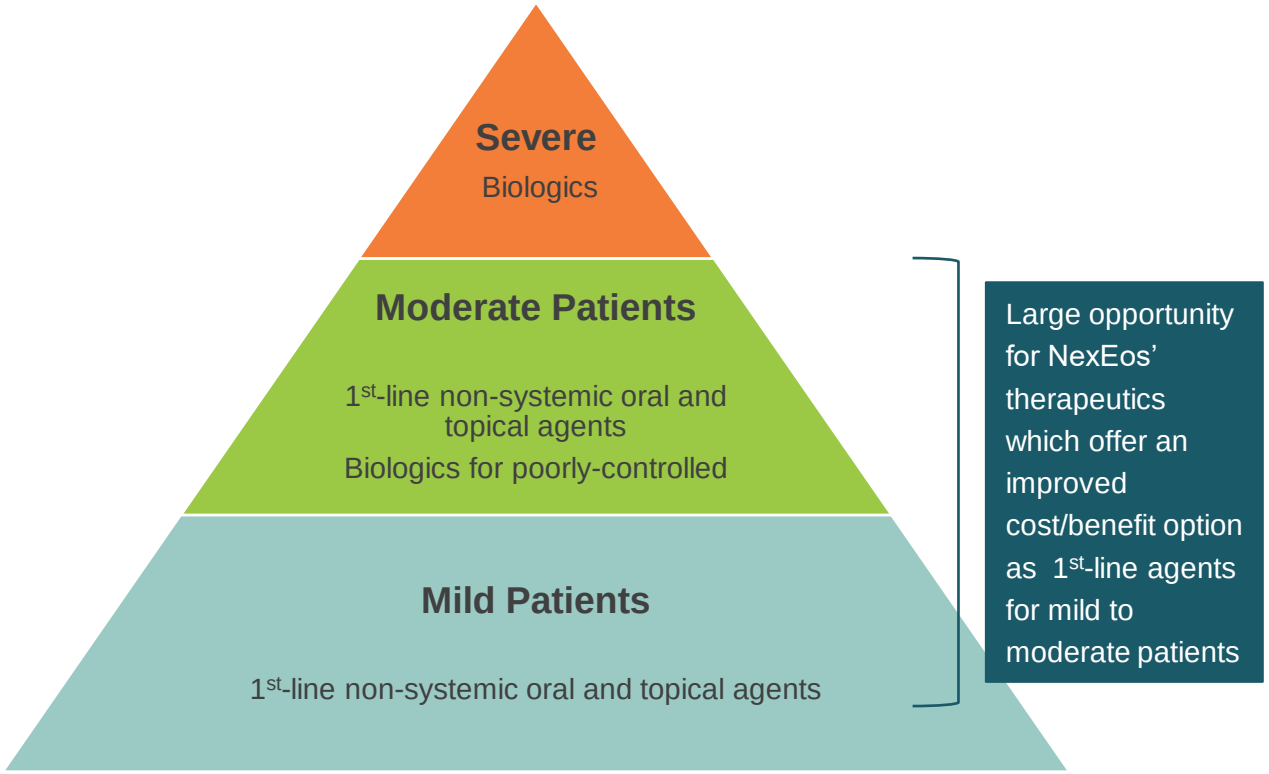


Current biologic therapies offer compelling efficacy; however, they have a high cost and carry safety risks (hypersensitivity, injection reactions, and in some instances, risk of anaphylaxis, and concern regarding inhibition of the immune system)

Commercial Opportunity for Therapeutic Targeting Eosinophil-Driven Inflammation is Broad and Growing

Wide array of conditions to target; patient populations continue to grow with increase in awareness

- Awareness and diagnosis of eosinophil-mediated diseases are on the rise – building potential for new therapies targeting eosinophil-driven inflammation
- Sales of biologics to treat eosinophil-driven diseases forecasted to exceed $5 - 10B by 2022
- Large opportunity for non-systemic oral and topical treatments offering an improved cost/benefit option for 1st-line status in less severe patients
- Targeting combination of indications can conservatively support sales >$1B
- Provides synergistic addition to pipeline for companies with biologics in eosinophil space
  - 1st-line: NexEos non-systemic oral and topical agents for mild to moderate patients
  - 2nd-line: Biologics for severe or poorly controlled moderate patients
  - Clinical management of Asthma, RA, psoriasis, and atopic dermatitis are relevant market proxies for the eos disease market=> 1st-line less expensive, small molecules; biologics reserved for severe patients or moderate patients who do not achieve disease control on 1st-line agent
  - Labels across biologics reflect restriction to severe or poorly-controlled moderate disease



NexEos Robust Pipeline: Potential Across Spectrum of Eosinophil-Mediated Diseases

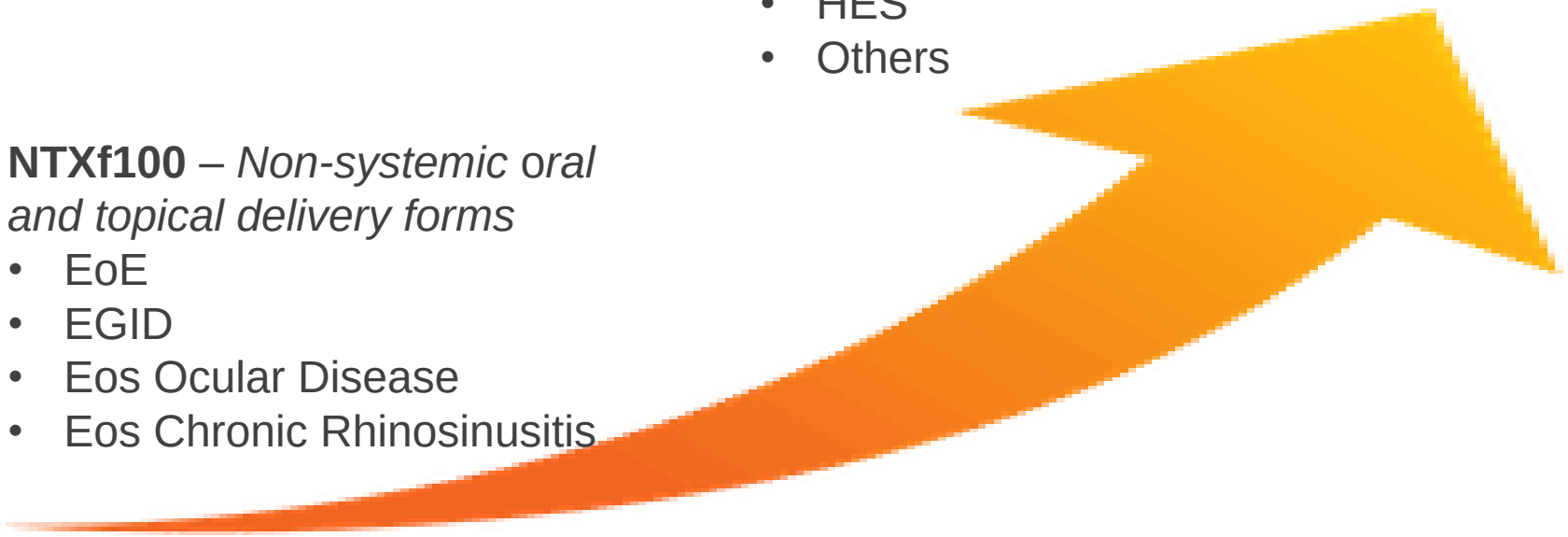
NTXf100 to offer significant opportunity with targeted delivery; next generation compound NTXp101 as injectable/inhaled allows for further expansion

NTXp101 – *Next generation; injectable/inhaled agent*

- Eos Asthma
- HES
- Others

NTXf100 – *Non-systemic oral and topical delivery forms*

- EoE
- EGID
- Eos Ocular Disease
- Eos Chronic Rhinosinusitis



Combination of indications for lead program (NTXf100) supports >$1B market opportunity. Expansion into next generation and systemic conditions further drives potential.

Lead program: NTXf100 will target administration (non-systemic oral, eye drops, nasal spray)

NTXp101: next generation treatment that further expands the potential reach into additional indications via injectable/inhaled administration

NexEos Bio

In Vivo Diagnostics

NDX33-o: Imaging Agent for the Diagnosis of Eosinophilic Esophagitis

Proof of Concept

NexEosBio™

NexEos Bio Diagnostics Opportunity

NDX33-o (radio-labeled heparin) for detection of eMBP1 inflammation in EoE

NDX33-o non-invasive imaging agent binds to eMBP1 and "lights up" eosinophil-related inflammation in the esophagus

- Heparin – most acidic (negatively charged) substance in the body binds to eMBP1 (strongly basic and one of the most positively charged substances[1])
- Well characterized agent with established pharmacokinetic and safety profiles; not systemically absorbed when taken as an oral solution
- Technetium^{99m} forms a stable complex with heparin (NDX33-o)
- Proof of concept demonstrated in initial study of 8 EoE patients
- Clearly defined regulatory path
- CMC supply for heparin established – US supplier
- Filed IND for NDX33-o
- Rapid path to market for lead diagnostic indication – EoE diagnosis and management
- NIH grant further validates science
- Strong granted IP – issued patents run through 2034; additional filings pending
- Granted Orphan Drug Designation for EoE; filed for Fast Track, pending IND opening

Scientific Advances

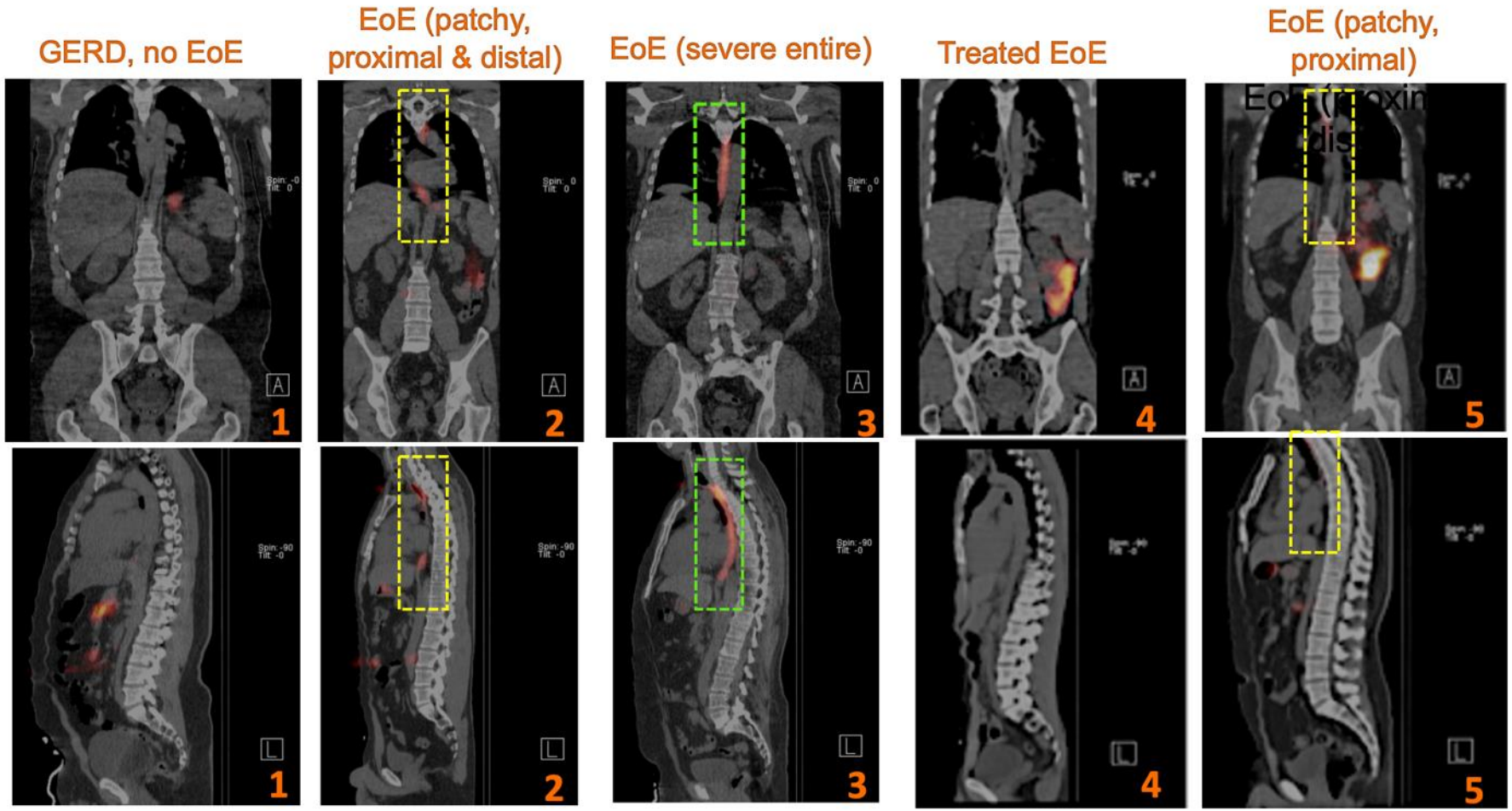
- *First, non-invasive and visual diagnostic for EoE*
- *Published on false negative for EoE biopsy vs positive read when targeting eMBP1 as marker[1]*
- *Using antibody for eMBP1 extra cellular detection in pathology, proving false negative patients can be positive for EoE Dx*

1. Saffari et. al, Mayo Clin Proc. 2020;95(3):449-458

Clinical Proof of Concept for NDX33-o

Successful imaging and mapping of inflammation by SPECT/CT (5 subjects)

Radioactivity localized to inflamed esophageal areas



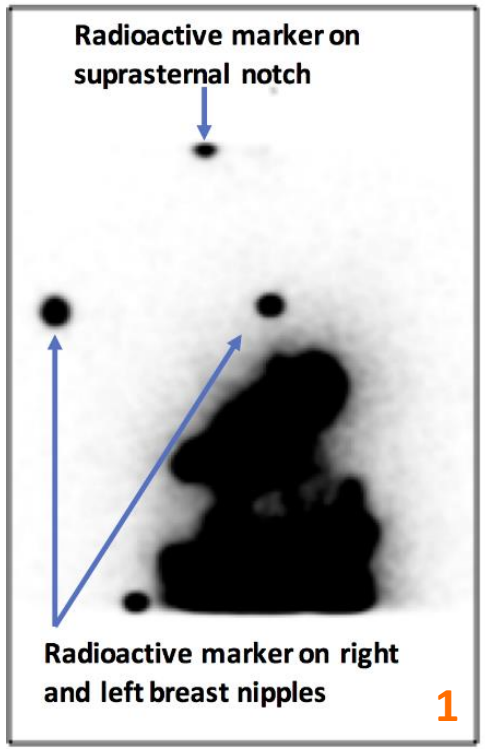
- Patients swallowed radio-labeled proprietary agent
- Imaging conducted by SPECT/CT
- Presence of disease was confirmed by subsequent EGD with biopsies per guidelines
- High correlation of imaging and biopsy results

NexEos Bio

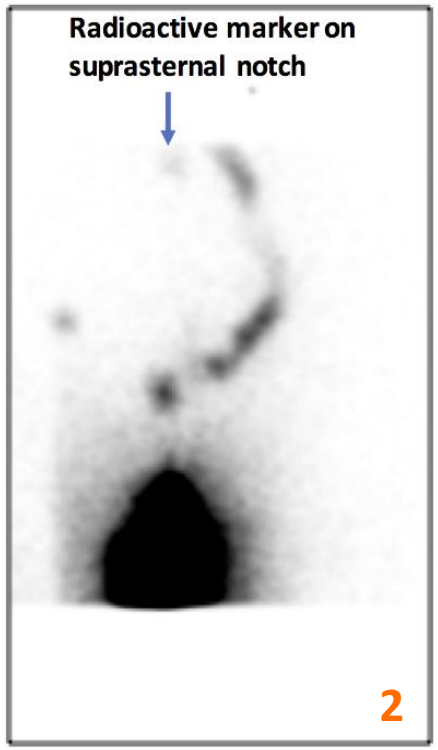
NDX33-o: SPECT Images of Same Five Subjects

- Enhanced visual detail
- Radioactivity counts

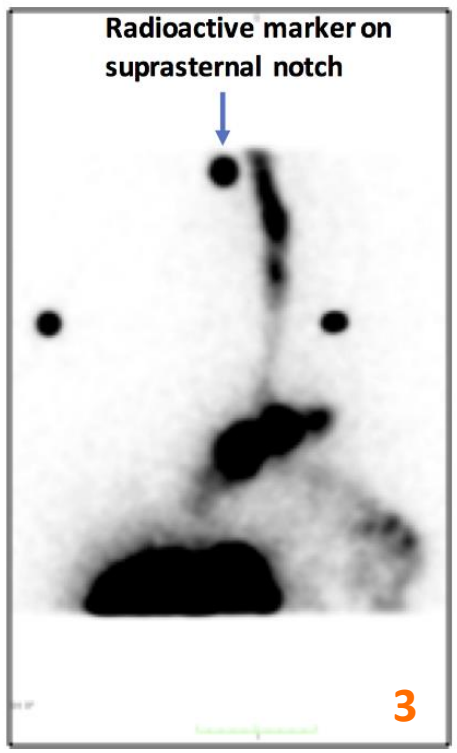
Unaffected with EoE



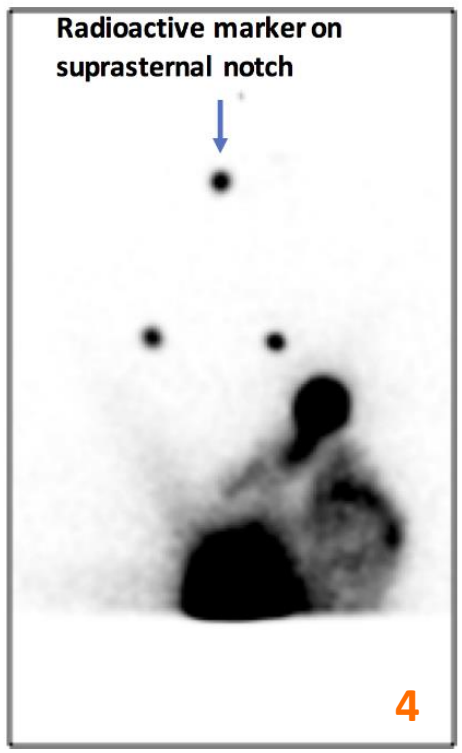
EoE (proximal, distal, slight mid)



EoE (severe entire, varying intensity)



Treated EoE



EoE (proximal)

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Proof of Concept Summary for NDX33-o

Preliminary results from the first clinical study in a total of eight* patients

- Swallowed NDX33-o binds to the esophagi of patients with active EoE
- NDX33-o binding correlates with markers of eosinophil-related inflammation in individuals with EoE
- Swallowed NDX33-o passed through the gastrointestinal tract with minimal absorption
- NDX33-o was well tolerated by all 8 patients
- The swallowed, radio-labeled formulation of NDX33-o has demonstrated:
  - Proof of Concept with a high degree of accuracy
  - Statistically significant correlations with severity and intensity of inflammation compared to biopsy
  - High degree of specificity and sensitivity support diagnostic approval probability
  - Visual analog assessments and dosimetry measurements correlate with eMBP1 deposition
- *Three patients studied at a lower dose – preliminary results mirror those of the initial 5 patients

NDX33-o: a novel diagnostic for eosinophil-mediated disease, including EoE

NexEos Bio

In Vivo Diagnostics

Commercial Opportunity: NDX33-o Imaging Agent for the Diagnosis of EoE

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Significant Unmet Need Exists in the Diagnosis and Ongoing Management of EoE

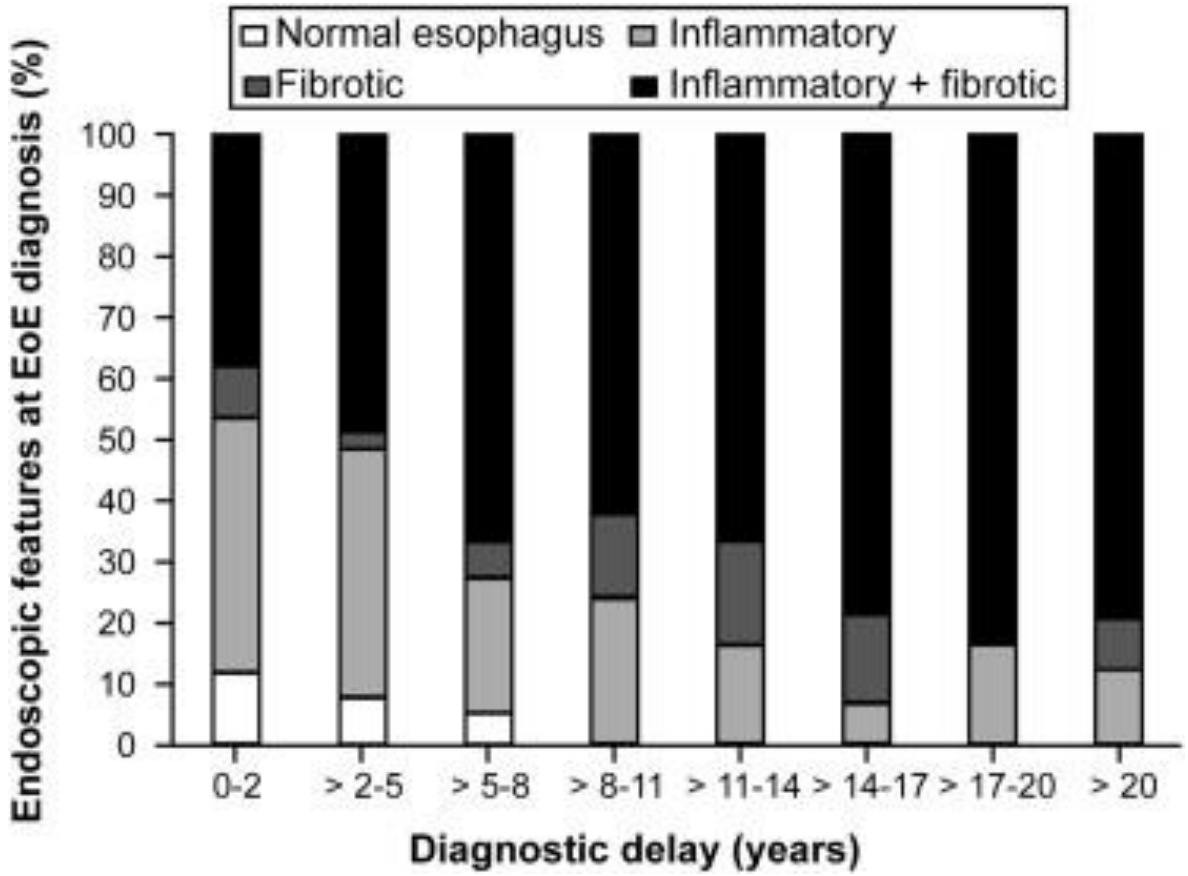
- Eosinophilic esophagitis (EoE) is a chronic inflammatory condition characterized by eosinophil infiltration into the esophagus
- Affects approximately 175,000 people in the US alone – likely underdiagnosed
- Current standard of care for diagnosis and ongoing disease management is endoscopy with biopsy
  - Guidelines require multiple biopsies to cover proximal and distal esophagus to identify eosinophils in target tissue
- The current standard has many shortcomings
  - Barrier to access – costly and resource intensive, invasive test that many patients are reluctant to undergo
  - Safety concerns across treated populations
    - in pediatrics, risk from general anesthesia used for sedation
    - in adults who have strictures, risk of esophageal perforation
  - EoE is a notoriously patchy disease – point specificity of biopsy often can miss areas of inflammation leading to misdiagnosis or underdiagnosis
- Delay in diagnosis drives long term sequelae of disease
  - Many patients have greater than a 5-year lag between onset of symptoms and diagnosis
  - Ongoing inflammation can lead to development of permanent fibrotic remodeling and strictures

NDX33-o: a non-invasive method of imaging the entirety of the esophagus

NexEos Bio

Delay of Diagnosis Leads to Disease Progression

Endoscopic features present at time of EoE diagnosis stratified by years since diagnosis[1]



- Mean diagnostic delay is up to 3.5 years in children and 8 years in adults based on a systematic review[2]
- The longer the diagnosis of EoE is delayed, the greater the inflammation duration
- Strictures are dependent on inflammation duration
- Missed or delayed diagnosis leads to higher costs related to disease progression (e.g. strictures)

1. Schoepfer AM, Safroneeva E, et al. Gastroenterol. 2013;145(6):1230–1236.e2
2. Shaheen NJ, Mukkada V, Eichinger CS, et al. Dis Esophagus. 2018;31(8):1-14.)

NexEos Bio

Commercial Potential for NDX33-o

First non-invasive imaging test for eosinophil-driven inflammation

Potential Benefits of Lead Diagnostic NDX33-o

Diagnosis

More accurate, non-invasive diagnostic approach, enables patients to be more quickly diagnosed, properly treated

Follow-up

Effective way to evaluate whether an EoE drug is working. This can reinforce patient's confidence and acceptance of the drug therapy, improve patient compliance, improve follow on disease management and ultimately improve the patient's quality of life.

Treatment Screening

This diagnostic technique can identify therapies that are less effective and allow for quick course correction which can ultimately reduce adverse effects for patients and potentially be more cost effective.

Significant upside potential >$500 million on expansion into other opportunities

Beyond the diagnosis of EoE: NDX33-o has the potential to identify and diagnose other eosinophil-related diseases, such as eosinophilic gastrointestinal disorders (EGID), including eosinophilic colitis and eosinophilic gastroenteritis; plus, eosinophilic rhinitis

Base forecast estimates range of $125 - $200 million revenue, US only

NexEos Bio

Development Plan for Diagnostic and Therapeutic Programs

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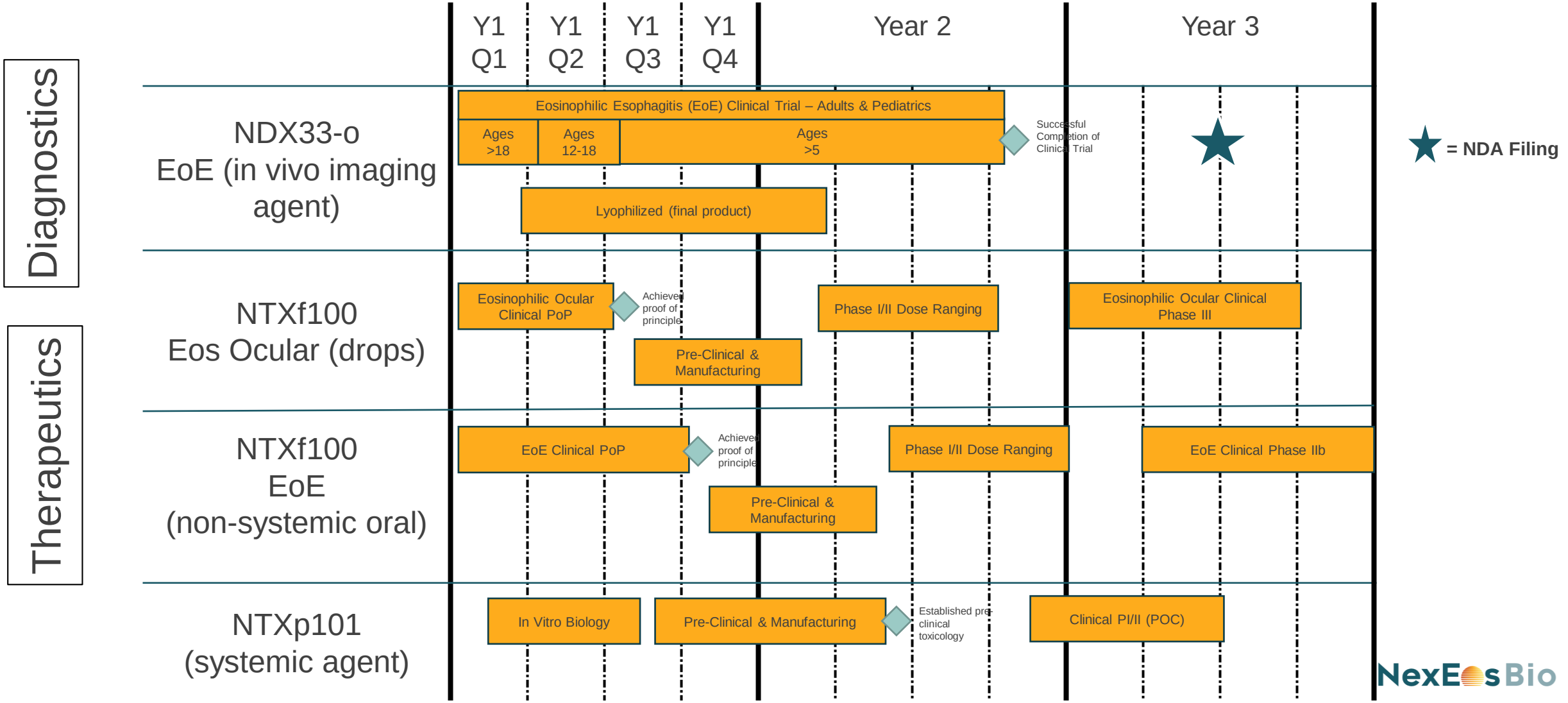
NexEos Bio: 3-Year Development Plan & Milestones



Regulatory Considerations: Diagnostic Program

NDX33-o has a clearly defined regulatory path

- Medical imaging agents are governed by the same regulations as other drug and biological products
- FDA approval path
  - Filed IND for NDX33-o
  - Granted Orphan Drug Designation for EoE diagnostic
  - Fast Track Designation will be considered upon approval of the IND
  - Subsequent submission of an NDA through CDER division
- Radiopharmaceutical “cold” kits consist of the active pharmaceutical ingredients (API) that do not contain radioactivity
  - NDX33-o “cold” kit contains sterile-pharmaceutical preparation of USP heparin, along with an adequate quantity of reducing agent, buffer, stabilizing agents and excipients
  - Technetium^{99m} (Tc-99m) will be added, prior to the diagnostic imaging test, at the radiopharmacy
- Established safety profiles
  - Both heparin and short-lived Tc-99m are well characterized agents with known pharmacokinetic and safety profiles
  - Heparin is not systemically absorbed when taken as an oral solution
  - Radiopharmaceuticals based on Tc-99m are the most used SPECT imaging agents in the clinic, accounting for >70% of diagnostic imaging for bone, renal, hepatic, hepatobiliary, cardiac, and oncological diseases[1]
    - Advantages of utilizing the Tc-99m isotope include a 6-hour half-life and administration to patients in low doses
- CMC supply for heparin established – US supplier

1. Boschi et al. 2019

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Regulatory Considerations: Therapeutic Program

Proposed NTXf100 and NTXp101 regulatory paths

- FDA approval path
  - Establish proof of principle for each NCE
  - Following established proof of principle, file INDs for both NCEs
  - Subsequent submission of NDAs through CDER division
- Lead therapeutic program (NTXf100) is a proprietary, fractionated high molecular weight subtype of heparin to be used as a non-systemic oral solution and/or eye drop
  - Well characterized agent
  - CMC supply established – US supplier
- Next Generation product (NTXp101) will allow for systemic and inhaled administration
  - Will require in vitro biology and pre-clinical toxicology

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Thank you!

Appendix

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Therapeutics

eMBP1: A New Target in Treating Eosinophil-Mediated Inflammation

Preclinical Evidence

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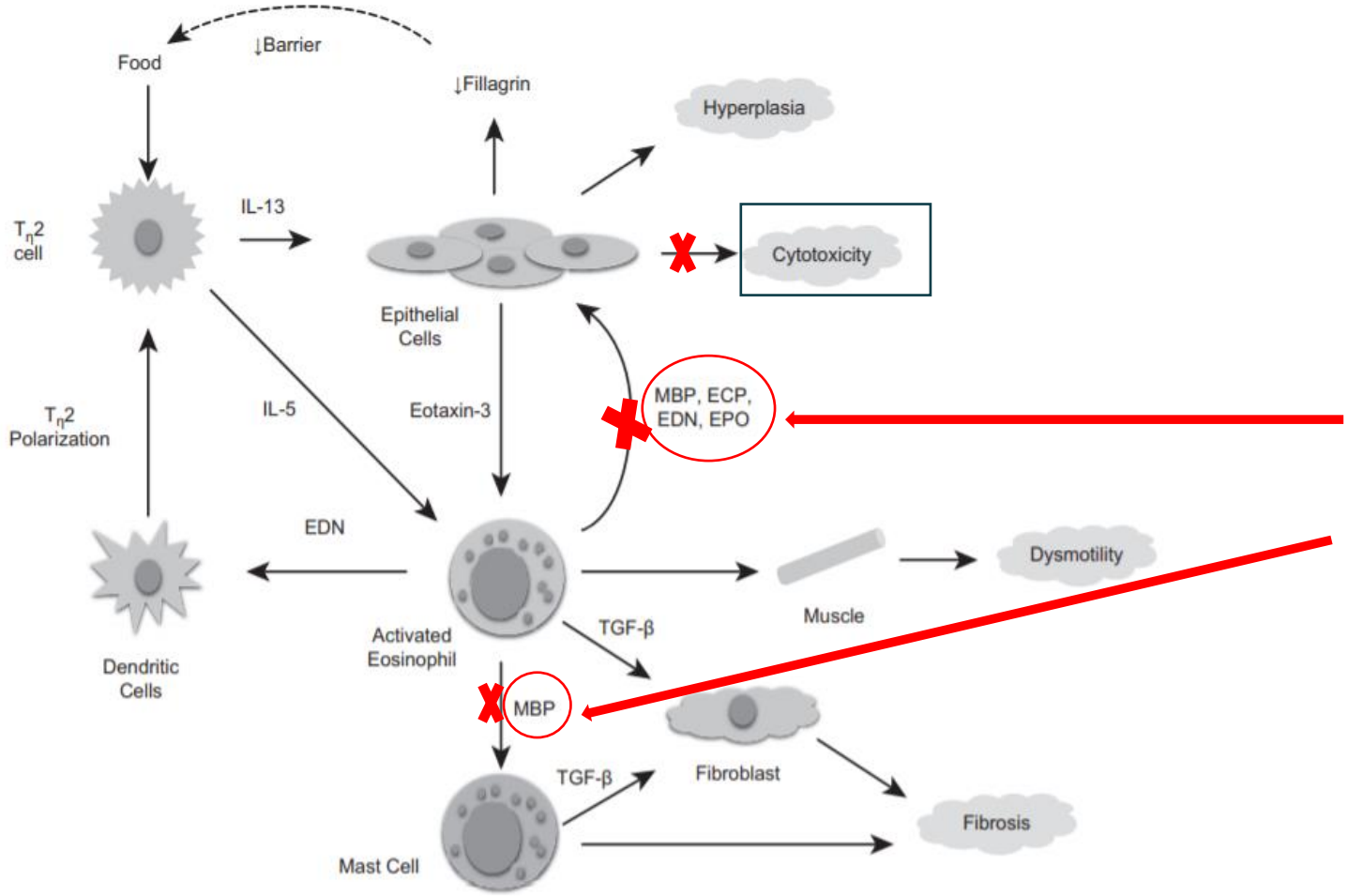
eMBP1 Neutralization: Blockade of Eosinophil Granule Products Demonstrate Anti-Inflammatory Effects



Neutralization of eosinophil granule products reduces cytotoxicity and therefore inflammatory effect on epithelial tissues and cells

Adapted from: Davis BP, Rothenberg ME. Eosinophils and Gastrointestinal Disease. In: Lee JJ, Rosenberg-HF.,editors. *Eosinophils in Health and Disease*. Waltham, MA. Academic Press, Elsevier 2012. p 484-493

eMBP1 Demonstrates a Highly Toxic Effect and Drives Inflammation

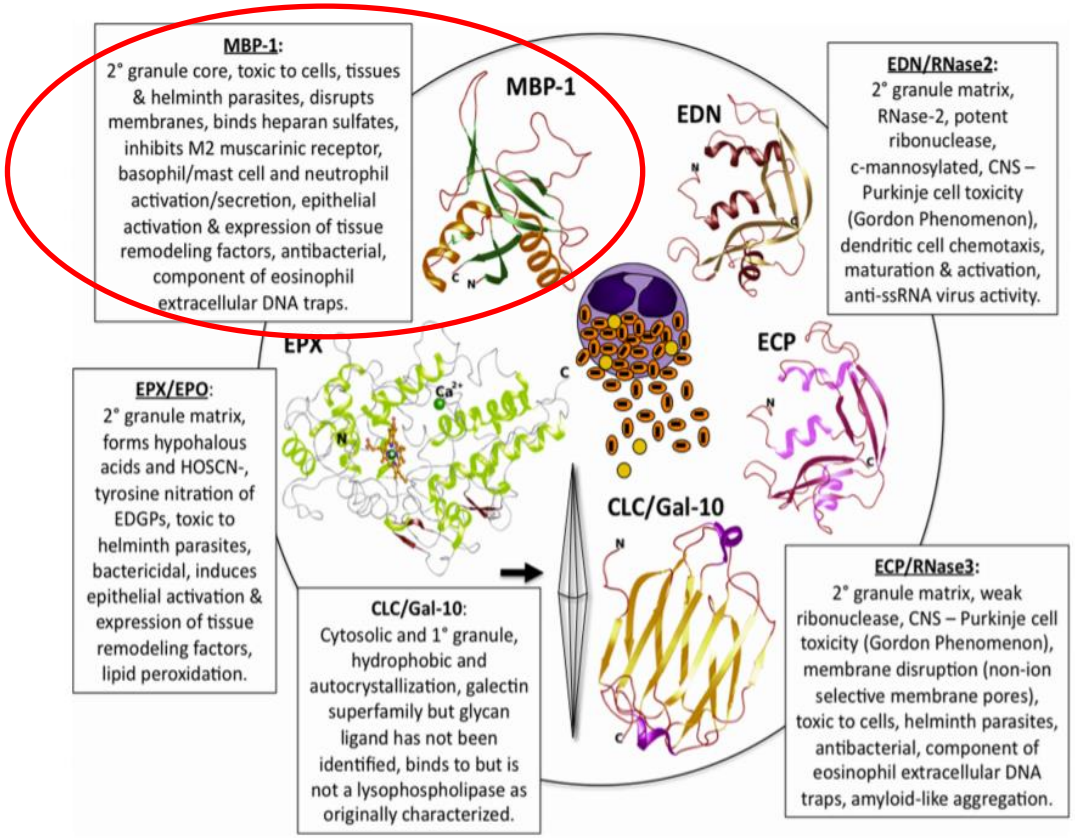
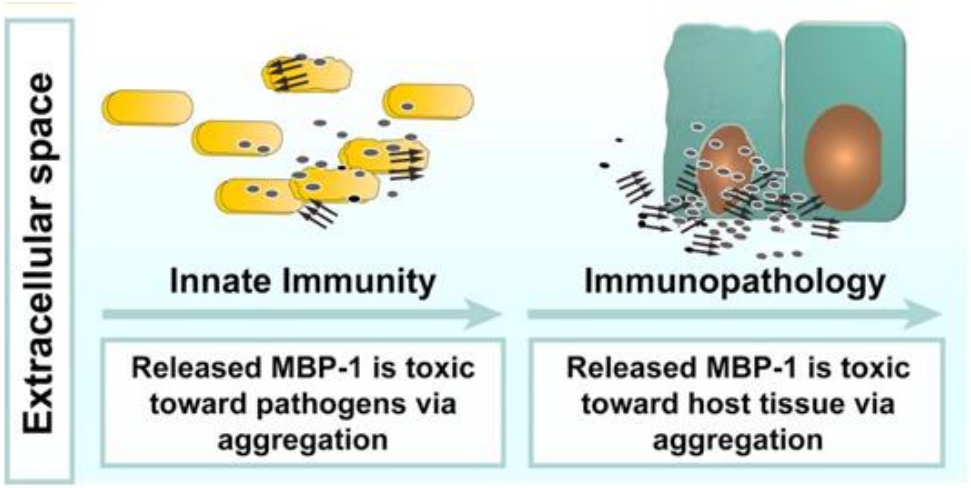


FIGURE 1. **Structural representations of the human eosinophil granule proteins showing their location and known functions.** The cationic granule proteins shown are: MBP-1 (Protein Data Bank (PDB) code 1H8U); EDN (RNase-2) (PDB code 1HI2); ECP (RNase-3) (PDB code 1QMT); and EPX/EPO) (based on molecular modeling using a myeloperoxidase structure, PDB code 1D2V). Also shown is CLC/Gal-10 (PDB code 1LCL), which is mainly cytosolic but also present in a small residual population of primary large core-less granules in the mature eosinophil. CLC/Gal-10 forms the hexagonal bipyramidal crystals (*arrow*) considered a hallmark of eosinophilic inflammation in tissues and body fluids in eosinophil associated diseases.

Adapted from: Acharya KR and Ackerman SJ. Eosinophil Granule Proteins: Form and Function. Journal of Biochemistry.2014;289:25: 17406-17415

- Since the late 1970s, research has linked the toxic role of eMBP1 to cell damage and inflammatory diseases
- eMBP1 and other inflammatory mediators are primary mechanisms of epithelial tissue damage and dysfunction



Major basic protein 1 (MBP-1) toxicity is restrained via crystallization in eosinophil secretory granules. Following eosinophil degranulation, eMBP1 toxicity is activated upon extracellular release and aggregation, which mediates the damage to pathogens and host cells. Image adapted from: Soragni et al. 2015.

Butterworth, et al. 1979; Kierszenbaum, et al. 1981; Gleich, et. al. 1979; Swaminathan et al. 2005; Acharya et al, 2014

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eMBP1 and Other Granule Proteins Facilitate Epithelial Damage and Bronchoconstriction in Asthma

- eMBP1 in the airway damages bronchial epithelial cells
- In vitro studies show the application of eMBP1 to respiratory tissue, at concentrations consistent with values found in sputum and bronchoalveolar lavage (BAL) fluid of asthmatic patients, leads to erosion of tracheal epithelium seen in the bronchial mucosa of subjects with asthma
- Autopsy specimens from patients who have died of asthma show eMBP1 deposited in the airway and on bronchial epithelium
- eMBP1 alters nerve function in animal models in the lung, inhibiting nerves which control airway responsiveness

TABLE 13.4.1 Eosinophil-Derived Inflammatory Mediators

		Cytotoxicity	Epithelial Damage	Airway Hyper-Responsiveness	Broncho-Constriction	Mucus Production, Vascular Leakage, Vasodilation	Eosinophil-Attraction Activation	Mast-Cell Proliferation
Granule proteins	MBP	+	+	+				
	ECP	+	+	+				
	EDN	+	+	+				
	EPO	+	+					
Lipid mediators				Leukotrienes C_4, D_4, E_4	+	+		
				Prostaglandin E2, I2	–	+		
				PAF	+			
Cytokines						IL-3	+	+
						GM-CSF	+	
						IL-5	+	

GM-CSF, granulocyte-macrophage colony-stimulating factor; IL, interleukin; PAF, platelet-activating factor.

Adapted from: Thomas A, Busse WW (2013). The Evolving Role of Eosinophils in Asthma. In: Lee JJ, Rosenberg HF editors. *Eosinophils in Health and Disease*. Waltham, MA: Academic Press, Elsevier; 2012. p. 448-460

Overall, these findings argue that eMBP1 is a key mediator in bronchial tissue damage and the clinical symptomology observed in asthma

Gleich GJ, Frigas E, Loegering DA, Wassom DL, Steinmuller D. J Immunol 1979;123:2925e7; Wardlaw DF, Dunnett S, Gleich GJ. Am Rev Respir Dis 1988;137:62

NexEos Bio

In Both Rat[1] and Primate[2] Models, eMBP1 Drives an Increase in Airway Responsiveness and Bronchoconstriction

	RAT MODEL		PRIMATE MODEL
Baseline	Dose-response characteristics to inhaled methacholine (MDRC) determined and the rats were allowed to recover	Baseline	Respirations (R_{rs}) monitored for 15 min followed by determination of methacholine dose-response characteristics in primates
Experimental Group	• Application of 100 µg of purified human MBP via direct instillation into the trachea • 1 hour after instillation, the MDRC were again assessed • 48 hours after MBP instillation airway responsiveness to methacholine reassessed, by which time airway responsiveness had returned to baseline level	Experimental Group	• Purified eosinophil-derived granule protein slowly infused into trachea via 20cm piece OE 240 tubing attached to syringe • Vehicle control challenge performed prior to administration of increasing doses of methacholine for construction of methacholine dose-response curves • Changes in R_{rs} measured at 1- and 3-min post aerosol challenge; with aerosol challenges separated by 5-8 min or R_{rs} returned to baseline
Control Group	Animals received buffer from void volume pool of same chromatography column used to purify MBP	Control Group	Animals received vehicle molecule and were monitored 1, 2, and 4 hours post instillation for determination of methacholine dose-response relationships
Conclusions	Within 1 h of direct instillation of MBP onto the trachea of rats, significant, ***short-lived increases in airway responsiveness to methacholine occurred analogous to the <u>lung dysfunction observed in asthmatic patients</u>***	Conclusions	• Direct instillation of MBP into the trachea of primates resulted in a ***<u>significant and dose-related increase in airway responsiveness to inhaled methacholine</u>*** • ***MBP and eosinophil peroxidase (EPO) induced a transient bronchoconstriction with resolution within 1-hour post-instillation***

1.Uchida DA, Ackerman SJ, Coyle AJ, Larsen GL, Weller PF, Freed J, et al.. Am Rev Respir Dis 1993;147:982e8
2.Gundel RH, Letts LG, Gleich GJ: J Clin Invest 87:1470-1473, April 1991

NexEos Bio

Pretreatment with *Antibody to eMBP1 P*revents Airway Hyperresponsiveness: Antigen-Challenged Guinea Pig Model

Sensitization and antigen challenge

- Intraperitoneal injections of 0.3ml ovalbumin every other day for total of 3 injections
- Antigen challenge → 3wks post last injection with aerosolized 5.0% ovalbumin for max 5 min until signs of respiratory distress

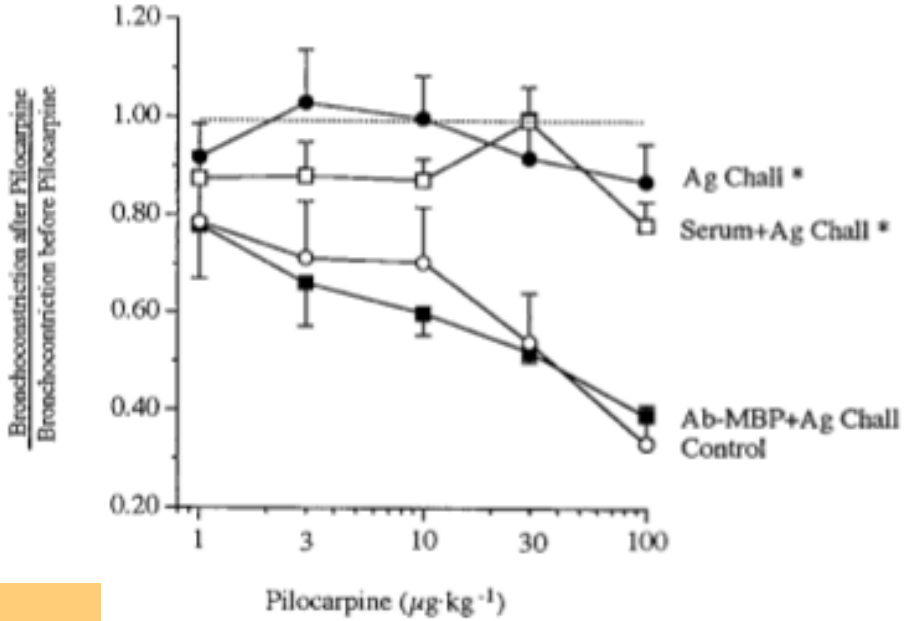
1.0ml Ab-MBP (rabbit anti-guinea pig eosinophil MBP) i.p. 18-24 hrs **BEFORE** antigen challenge

Pretreatment Regimen

1.0ml Ab-MBP (rabbit anti-guinea pig eosinophil MBP) i.p. 18-24 hrs **AFTER** antigen challenge

Neuronal M_2 muscarinic receptor function tested with administration of pilocarpine. Effects on vagally-stimulated bronchoconstriction evaluated

Pretreatment with Ab-MBP (1.0ml intraperitoneal) protected response to bronchoconstriction



Airway hyperresponsiveness and consequent bronchoconstriction is a result of neuronal M_2 muscarinic receptor function **inhibition by eMBP1**

Evans et al. J. Clin. Invest. 1997. 100:2254– 2262.

NexEos Bio

In Vivo Diagnostics

Back ups: Proof of Concept for NDX33-o Imaging Agent for the Diagnosis of EoE

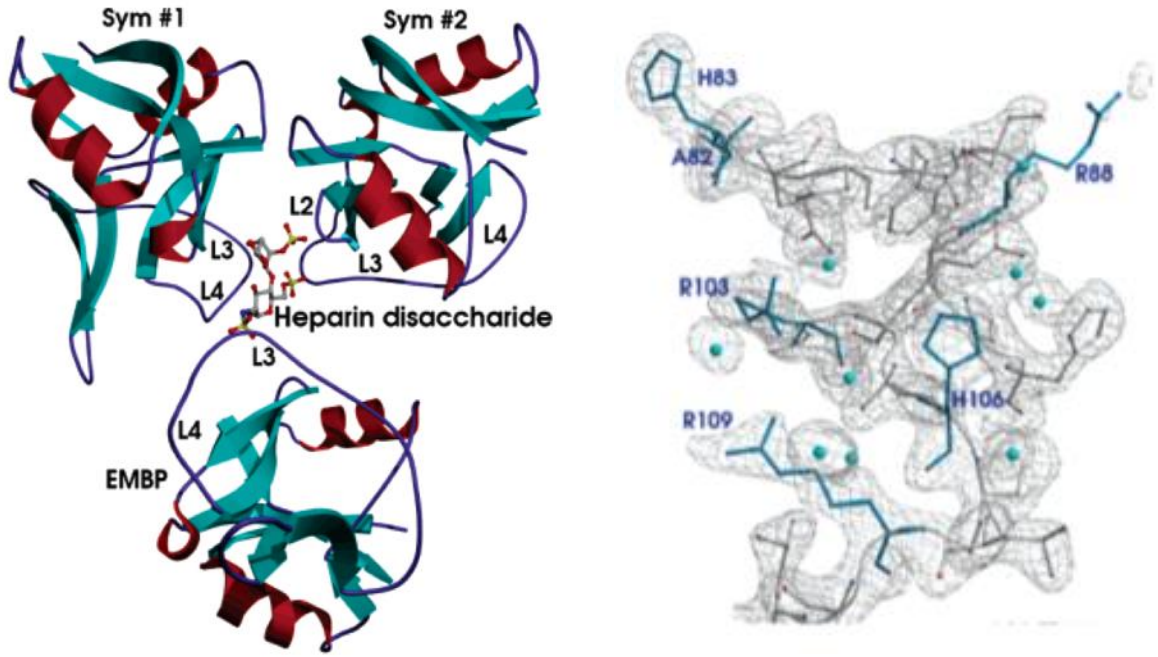
NexEosBio™

Neutralizing eMBP1 Interrupts Inflammation Demonstrating the Basis of a Treatment Effect on Eosinophilic-Driven Diseases

Unfractionated heparin in our therapeutic model is shown to neutralize eMBP1 in vitro and in vivo

- **In vitro**: Heparin binds to eMBP1 and blocks eMBP1 destruction of *helminth parasites* therefore demonstrating a neutralizing effect and the potential to reduce inflammation caused by eosinophil granule proteins

- **In vivo**: Heparin binds avidly to a specific site on eMBP1
  - The effects of eMBP1, strongly bound to cardiac and lung M2 muscarinic receptors, **can be reversed** by bound heparin further illustrating the neutralizing effect of heparin on eosinophilic-driven inflammatory processes



Interaction of a single molecule of heparin disaccharide with molecules of eMBP1

Swaminathan GJ, Myszka DG, Katsamba PS, Ohnuki LE, Gleich GJ, Acharya KR. Eosinophil-granule Major Basic Protein, a C-type Lectin, Binds Heparin. Biochemistry. 2005;44:14152

Butterworth, et al. 1979; Kierszenbaum, et al. 1981; Jacoby DB, Gleich GJ, Fryer AD. 1992

NexEos Bio

EoE: NDX33-o (Heparin-^{99m}Tc) Binding and Inflammation Scores

Patient No.	Disease State	Hep-Tc Binding Visual Scoring (P, M, D)*	Eosinophil Counts/HPF (P, M, D)	Esophagus Geometric Counts of Planar Images **	eMBP1 Immunostaining Findings (P,D)
1	Normal	0, 0, 0	(0,0,0)	6,626	(Negative, Negative)
2	EoE	2, 1, 3	(0,5,42)	18,363	(1/2+, 2-3+)
3	EoE	4, 4, 2	(80, 125,143)	66,323	(3+, 3+)
4	EoE	0, 0, 0	(0,0,0)	5,010	(Negative, Negative)
5	EoE	2, 1, 0	(91,32,0)	16,010	(1/2+, 1/2+)

* P, M, D = proximal, mid, distal

** Geometric mean counts from anterior and posterior planar images 2 hrs after oral administration, with the region of interest of approximately equal size

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NDX33-o: Correlation Analyses - Spearman's Rho

Very high correlation between biopsy and imaging results

	Peak Eosinophil Counts (P, M, D)	eMBP1 Scores (P, D) ##
Visual (Heparin-Tc99m) binding (P, M, D) *	$r_s = .84$ $p < 0.001$	$r_s = .87$ $p = 0.001$
Geometric Counts of Planar Esophagus Images **	$r_s = .87$ $p = 0.054$	$r_s = .98$ $p = 0.005$

P values range from (0.001-0.054) depending on which correlating measure is being compared.

* P = Proximal, M = Mid and D = Distal esophageal segments
** Geometric mean counts from anterior and posterior planar images two hours after oral administration.
eMBP1 immunostaining score by immunofluorescence localization

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In Vivo Diagnostics

Back ups: Logistics for NDX33-o Imaging Agent for the Diagnosis of EoE

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Logistics for NDX33-o are Fairly Straightforward

Heparin manufacturer prepares lyophilized (stable) heparin

"Cold" kits: Contract GMP manufacturer assembles cold kits for radiolabeling -- lyophilized heparin, stabilizing agents and excipients

Cold kits stored in radiopharmacy until needed. **Shelf life to be determined based on development data.**

Day of Test Radiopharmacist adds tech^{99m} to cold kit to create NDX33-o

Day of Test Patient sips NDX33-o prior to SPECT/CT scan

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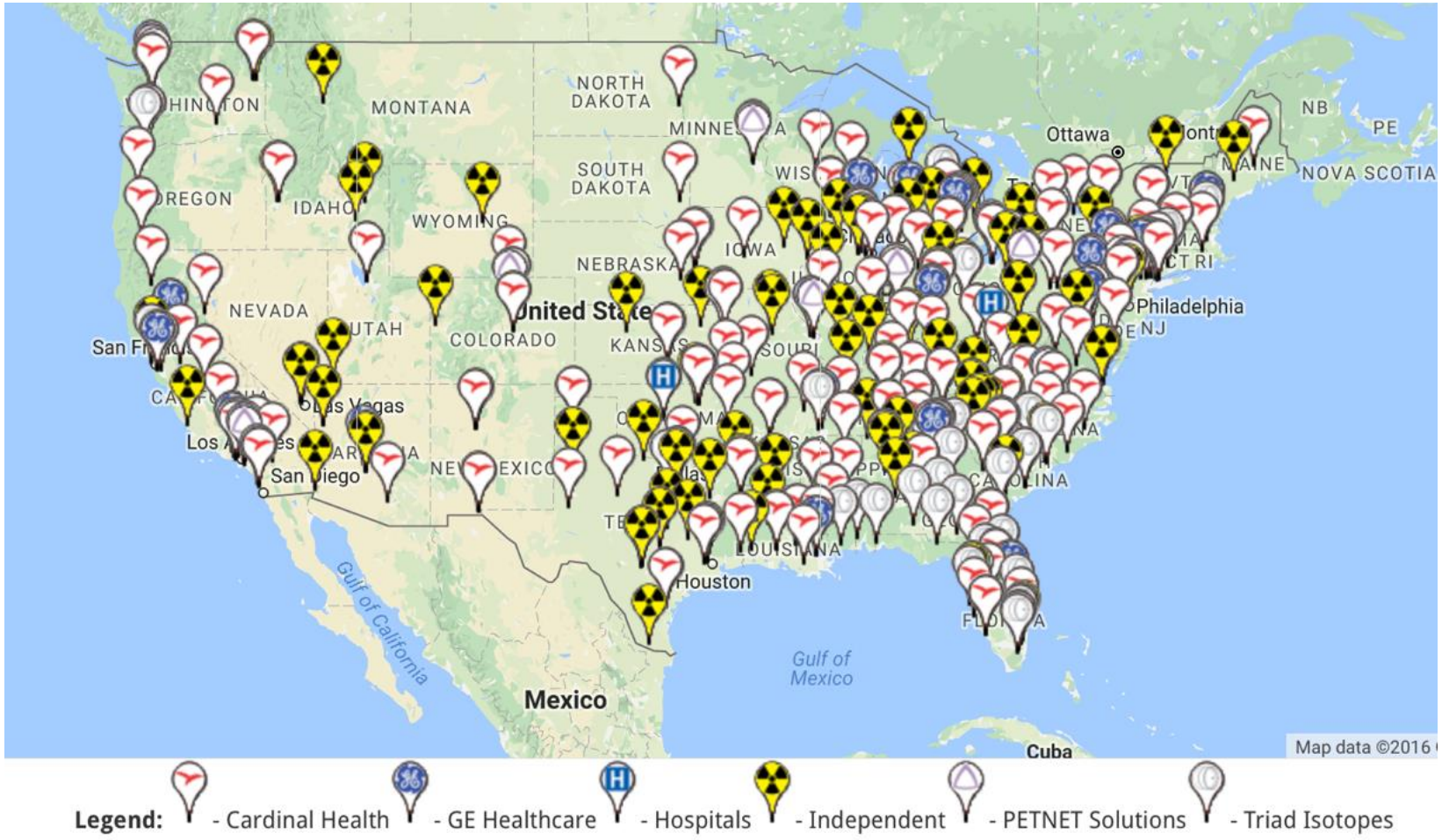
Radiopharmacies are a Manageable Target in the U.S.



# of Radiopharmacies in the U.S.

- Cardinal Health – 130
- UPPI – 66
- Independent – 64
- Triad Isotopes – 61
- PETNET Solutions – 41
- GE Healthcare – 19

Approximately 400 total radiopharmacies within the U.S.

Department of Pharmacy Practice, Nuclear Pharmacy Program, Purdue University, West Lafayette, IN